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Pulmonary Perspective

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Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

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KEY TO ACRONYMS

AGE: advanced glycation end products

AM: Alveolar macrophages

BALF: Bronchoalveolar lavage fluid

B-MSCs:mesenchymal stem cells

B-HSCs: hematopoietic stem cells

DCs: Dendritic cells

ECM: Extracellular matrix

EDA: fibronectin isoform extra type III domain A

FPF: familial pulmonary fibrosis

HDAC: histone deacetylases

NF-κB: Nuclear Factor Kappa B

Nk: Natural killer

PBLs: Peripheral blood leukocytes

ROS: Reactive Oxygen Species

SA- ß-gal: senescence-associated ß-galactosidase

SIRT-1: Sirtuin-1

SMP30: Senescence marker protein 30

TL: Telomere lenght

RAGE: receptor for advanced glycation end products

TLR: toll-like receptor

ABSTRACT

Aging is a natural process characterized by progressive functional impairment and reduced capacity to respond appropriately to environmental stimuli and injury. The incidence of two common chronic respiratory diseases (chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)) increases with advanced age. It is plausible, therefore, that abnormal regulation of the mechanisms of normal aging may contribute to the pathobiology of both COPD and IPF. This review discusses the available evidence supporting a number of aging mechanisms, including oxidative stress, telomere length regulation, cellular and immunosenescense, as well as changes in a number of anti-aging molecules and the extra-cellular matrix are abnormal in COPD and/or IPF. A better understanding of these abnormalities may help the design of novel and better therapeutic interventions for these patients.

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INTRODUCTION

Aging is a natural process characterized by progressive functional impairment and reduced capacity to respond appropriately to environmental stimuli and injury (1). As any other organ, the lungs also age. Physiological lung aging is associated with several anatomic (enlargement of alveoli without alveolar wall destruction, reduced surface area for gas exchange and loss of alveolar attachments supporting peripheral airways, often referred to as "senile emphysema") and functional changes (reduced elastic recoil and increased gas trapping) (2), that result in a progressive decrease of expiratory flow rates with age in otherwise healthy people (3).

On the other hand, epidemiological studies indicate that aging is associated with an increased incidence of a variety of chronic diseases, including atherosclerosis, type2 diabetes mellitus, osteoporosis, cancer, auto-immunity and neurological diseases. The lungs are no exception since the incidence of two common chronic respiratory diseases (chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)) also increase with age (4-6). Interestingly, although COPD and IPF are distinct disease entities, they share some similarities. Both occur later in life(4, 5), both are punctuated by episodes of “exacerbations” that are often of unclear origin(7, 8), and both are characterized by enhanced deposition of collagen and fibrosis (although, admittedly, this occurs in different locations in each disease, in the small airways in patients with COPD, and in the lung parenchyma in IPF). Finally, interestingly, both conditions can coexist in the same patient (9). It is

plausible, therefore, that abnormal regulation of the mechanisms of normal aging may contribute to the pathobiology of both COPD and IPF (10).

The cellular and molecular mechanisms of physiological aging are still not well understood (11). Oxidative stress, telomere length regulation, cellular and immunosenescense, as well as changes in a number of anti-aging molecules and in the extra-cellular matrix are thought to be key mechanisms (11). This review discusses the available evidence that these mechanisms are abnormal in COPD and/or IPF (Table 1) and can therefore contribute to the pathogenesis of both diseases.

OXIDATIVE STRESS

The term “oxidative stress” refers to molecular, cellular and tissue changes induced by the accumulation oxidative damage which, in turn, may be the end-result of the excessive production of reactive oxygen species (ROS) and/or defective antioxidant responses. The respiratory chain in the mitochondria is an important endogenous source of ROS, whereas cigarette smoke is an important source of exogenous oxidants.

Oxidative stress is believed to play a key role in aging (12) since oxidative changes provide mechanistic switches to control protein conformation, catalytic activity, protein-protein interactions, protein-DNA interactions, and protein trafficking. Other signaling mechanisms can be altered by oxidative stress

including the induction of nuclear factor kappa B (NF-κB)and Smad3, transcription factors also known for their ability to promote changes in the expression of matrix proteins by increasing collagen deposition.

Patients with COPD have evidence of oxidative stress in the lungs, blood (13) and skeletal muscle, where mitochondrial dysfunction resulting in the excessive production of ROS and oxidative damage to mitochondrial DNA (14, 15) have been described. Importantly, oxidative stress is considered to be a key mechanism in many of the pathogenic processes in COPD (16). Likewise, patients with IPF also have increased markers of oxidative stress both locally in the lungs and systemically (17). In particular, they have evidence of an altered glutathione redox system with deletion of reduced glutathione in the alveolar lining fluid (18).

Jones *et al.* proposed that the traditional view that oxidative stress is a global imbalance of pro-oxidants and anti-oxidants is inadequate and conceptually limiting (19). The new concept is that oxidative stress cannot be defined by a single, global balance because multiple, independently regulated, thiol/disulfide control systems exist (19). So, in the absence of deficiency, shifting the pro-oxidant/antioxidant balance by providing more antioxidants provides little increased protection against disease processes associated with aging. This can explain why numerous interventional trials with antioxidants have been inconsistent and inconclusive(19). Anti-oxidant therapy remains controversial in the management of COPD and IPF.

TELOMERE LENGTH REGULATION

Telomeres are regions at the ends of chromosomes containing 1-5kb of (TTAGGG) repeats which protects DNA against degradation and recombination, thus supporting chromosomal stability (20). In most somatic cells telomeres shorten with every cell cycle because of the difficulty in priming DNA synthesis by DNA polymerase in this region. Telomere length therefore reflects the length at birth and its rate of attrition thereafter. The latter is as a result of replication history, but also a reflection of a number of factors, such as cumulative oxidative stress and chronic inflammation (21), acting on progenitor cells (see below). Abnormalities in TL have been described both in COPD and IPF.

In circulating leukocytes, current and former smokers had shorter telomeres than did age-matched nonsmokers (22), there is a dose-dependent relationship between TL and the years smoked (23) and TL in COPD patients is shorter than that of control subjects in any age range (24). Other studies have shown shorter telomeres in the lungs of COPD patients, particularly those with emphysema (25, 26). Experimental animals with shorter telomeres in their lung cells have an increased susceptibility to cigarette smoke-induced emphysema (27).

In patients with IPF, short telomeres in lung epithelial cells and peripheral blood cells have also been identified(28, 29). Interestingly,10% of patients with familial pulmonary fibrosis (FPF) have mutations of one of the two key factors

involved in telomere lengthening: the reverse transcriptase component (TERT) and the RNA template component (TERC)(30). In addition, around 20% of patients with *dyskeratosis congenita*, a genetic disease caused by telomerase mutations, develop pulmonary fibrosis (31).

CELLULAR SENESCENCE

When TL reaches a critical value, a “DNA damage response” is activated, leading to cell-cycle arrest (senescence) and, eventually, apoptosis. Cell senescence is, therefore, the cellular equivalent of aging. A number of cellular and molecular mechanisms are associated with cell senescence, including: *(a)* persistence of active metabolism, loss of proliferative activity and resistance to apoptosis; *(b)*accumulation of DNA damage, impairment of DNA repair, epigenetic modifications of nuclear DNA and attrition of telomeres; and, *(c)*protein, nucleic acids and lipids damage from oxidative stress(32, 33). As a result, senescent cells enter an irreversible growth arrest, exhibit flattened and enlarged morphology and expresses a different set of genes, including the cell cycle control kinase inhibitors p53, p21 and p16(34). Cellular senescence and cell arrest can occur by *intrinsic* and *extrinsic* mechanisms. The former relate to the exhaustion of a predetermined proliferative capacity with erosion of telomeres (*replicative senescence*); the latter to the effect of external stresses, such as oxidative stress (*stress-induced premature senescence*).Cell senescence has been identified both in COPD and IPF.

In vitro exposure of human epithelial cells to cigarette smoke, the major etiological factor in COPD, results in changes in cell morphology indicative of cellular senescence, such as increased expression of senescence-associated ß-galactosidase (SA- ß-gal) and elevated p21 $^{CIP1/WAP1/sdi1}$protein (35).Similar increased expression of markers of cellular senescence were found in Type II alveolar epithelial cells in the lungs of mice exposed for three weeks to cigarette smoke associated with the accumulation of lipofuscin, indicating that stress-induced premature senescence had occurred (35).Likewise, increased markers of cellular senescence are also present in emphysematous lungs. For instance, the expression of the senescent associated markers p16^{INK4a} and p21$^{CIP1/WAP1/sdi1}$ are higher in Type II alveolar epithelial cells in the lungs of patients with emphysema than in control smokers and non-smokers(36). Cellular senescence can contribute to the pathogenesis of COPD through at least two, non-mutually exclusive, mechanisms. First, increased epithelial and endothelial cell apoptosis occurs in emphysematous lungs (37, 38). This is thought to results in loss of cells in the alveolar walls and, consequently, in emphysema. Compensatory mechanisms involving cell proliferation should occur to abrogate the loss of alveolar cell loss (lung maintenance program) (39). Yet, when cellular senescence occurs, cellular proliferation is lost and the balance is tipped towards apoptosis and the resulting formation of emphysematous lesions. Fibroblasts from lungs with moderate to severe emphysema also show increased SA-ß-gal (25)and reduced proliferation rates, which may affect such a lung maintenance program. Second, recent evidence suggests there is a close relationship between cellular senescence and inflammation. Senescent cells demonstrate activation of NFκB, a major

transcription factor in the regulation of inflammation. Senescent cells also release increased amounts of various inflammatory cytokines resulting in enhanced inflammation (40).These pro-inflammatory mechanisms associated with senescence have also been demonstrated in human lung tissue, where the expression of phosphorylated IkB and TNFα were found to be increased in $p16^{INK4a}$-positive Type II alveolar epithelial cells, suggesting that senescent alveolar cells promote inflammation at the cellular level. Further, there is also a relationship between the degree of $p16^{INK4a}$ -positive cell senescence and severity of inflammation in emphysema (41). Direct evidence supporting the association between telomere dysfunction, senescence and inflammation in lung tissue was also provided from telomerase deficient mice which exhibit shorter telomeres in lung cells and demonstrate increased lung tissue levels of pro-inflammatory mediators (41). This enhanced inflammation can increase protease release from cells and facilitate the development of a protease/antiprotease imbalance, which may in turn cause pulmonary emphysema to progress. Thus abnormal regulation of a number of mechanisms involved in normal aging is relevant to the pathogenesis of emphysema (Figure 1).

Abnormalities in cellular senescence have also been demonstrated in patients with IPF, particularly in bone marrow-derived stem cells. These cells can be divided in two groups: *(a)* hematopoietic stem cells (B-HSCs); and, *(b)* mesenchymal stem cells (B-MSCs). Both have been implicated in the pathogenesis of IPF. Fibrocytes are a subgroup of adherent B-HSCs that express stem and leukocyte cell markers like CD45 and CD34 and produce

type I collagen (42, 43). They have been shown to traffic to the lungs in response to CXCL12 and to contribute to the pathogenesis of IPF (44, 45). Furthermore, high levels of circulating fibrocytes have been shown to herald poor prognosis in IPF (46). Interestingly, aging mice are also characterized by a senescence-related increase in fibrocyte (and a parallel decrease of B-MSC) mobilization, higher serum levels of CXCL12 and increased concentration of TGF-βin the lungs (47).

On the other hand, B-MSCs are characterized by a quiescent state with low metabolic activity and are primarily in the G0 phase of the cell cycle(48). This quiescent state is maintained by both extrinsic and intrinsic mechanisms and has been postulated to be a way of preserving their long-term proliferative potential and genomic integrity. Conversely, DNA damage checkpoints and several repair pathways are cell cycle dependent, and the quiescent state of B-MSCs can underlie the propensity of these cells to accumulate DNA damage during aging, ultimately leading to a rapid stem cell depletion or exhaustion (Figure 2). Several studies indicate that B-MSCs can migrate and participate in lung repair by modulation of inflammation (49-51), but both physiological aging and pathologic senescence can alter these effects. For instance, administration of stem cells from young, but not from old mice, was reported to restore pathways critical for cardiac angiogenesis in senescent mice without prior bone marrow suppression (52-54). In a remarkable study, Conboy and coworkers demonstrated that hetero-chronic-parabiotic mice (two mice, one old and one young, surgically joined with shared circulatory systems) restored age-related loss of stem cell capacity in blood and liver of the older member of the pair(55).

Interestingly, senescent B-MSC increase the susceptibility to the development of fibrosis because of abnormal repair responses triggered in subjects exposed to tobacco, asbestos, and other agents known to stimulate DNA damage (56).

ANTI-AGING MOLECULES

Several anti-aging molecules influence the aging process and may therefore have relevance to the pathogenesis of COPD and IPF. *Senescence marker protein 30 (SMP30)*, which is expressed in the liver and kidneys, increases in early life and decreases progressively with age. SMP30 knockout mice have increased alveolar cell apoptosis and enlargement of the alveoli indicative of emphysema (57). Consistent with the role of oxidative stress in aging, the lungs of SMP30-/-mice show age-dependent increases in protein carbonylation (a marker of oxidative stress). Furthermore, chronic exposure of SMP-/- to cigarette smoke results in a greater degree of emphysema compared with SMP Wild-type mice, suggesting that aging in this model directly enhances the lung injury produced by cigarette smoke (58).

The *klotho* gene encodes a membrane protein that is a regulator of oxidative stress and cell senescence. Mice with a defect in the *klotho* gene have a short lifespan and develop a syndrome resembling aging with atherosclerosis skin atrophy, osteoporosis and emphysema (59). The development of emphysema in mice with a defect in the *klotho* gene is associated with activation of MMP-9 in the lungs which has also been implicated in smoking-induced emphysema (60).The role of the *klotho* protein in COPD has not yet been determined.

Metabolic nicotinamide adenine nucleotide (NAD)-dependent histone/protein deacetylases (*sirtuins*) play an important role in a variety of processes including stress resistance, metabolism, apoptosis, senescence, differentiation and aging. Sirtuins are Type III histone deacetylases (HDAC) and act on histone residues in DNA thereby mediating gene silencing. Sirtuin-1 (SIRT-1) is essential for maintaining silent chromatin via the deacetylation of histones, but in addition regulates NFκB-dependent transcription and cell survival in response to TNFα (61). Environmental stress, such as cigarette smoke exposure, decreases SIRT-1 levels in both macrophages in vitro and rat lungs in vivo associated with increased inflammatory cytokine expression (62). SIRT-1 has recently been shown to be reduced in lung cells from COPD patients as a result of post-translational oxidative modification of the molecule by cigarette smoke-derived oxidants, leading to increased acetylation and enhanced inflammatory responses to cigarette smoke (63).Thus SIRT-1 may have an important role in the regulation of inflammation in COPD as well as being involved in aging.

In addition to sirtuins, histone deacetylase 2 (*HDAC2*orType I HDAC) have been reported to be anti-aging molecules. Knockdown of HDAC2 induces cellular senescence by enhancing p53-depending trans-repression and trans-activation in target genes (64). HDAC2 has been shown to be reduced in the lungs of COPD patients compared to smokers who have not developed the disease (65) as a result of oxidative modification of the HDAC molecule (66, 67). Down-regulation of HDAC2 results in acetylation of histone residues,

unwinding of DNA and access of transcription factors such as NFκB to the transcriptional machinery resulting in transcription of pro-inflammatory genes. Histone modifications are also implicated in cell senescence. Prior to senescence, cells exhibit an increase in $p21^{Cip1/WAF1}$ which decreases when the cells reach senescence whilst expression of $p16^{INK4a}$ increases and this is thought to be responsible for the final, irreversible failure of proliferation. It has been shown that endothelial and alveolar type II epithelial cells in the lungs of emphysematous patients have increased expression of $p16^{INK4a}$ and $p21^{Cip1/WAF1}$(41).The expression of $p16^{INK4a}$ and $p21^{Cip1/WAF1}$ is partially controlled through histone acetylation within the promoter regions. This suggests a role for HDAC inhibition in senescence by controlling both $p16^{INK4a}$ and $p21^{Cip1/WAF1}$.

Finally, aging is also associated with the accumulation of *advanced glycation end products (AGE),* formed by non-enzymatic glycation and oxidation of proteins (68). AGE-formation changes the chemical and biological properties of proteins inside and outside of the cell. Binding to specific cell surface receptors induces activation of cellular signaling pathways leading to cellular dysfunction and cell death (69). The receptor for advanced glycation end products (RAGE) is a multi-ligand signal transduction receptor that can initiate and perpetuate inflammation. Its soluble isoform (sRAGE) acts as a decoy receptor for RAGE ligands, and is thought to afford protection against inflammation. sRAGE has been shown to be significantly lower in COPD patients than in controls and correlates with the severity of emphysema as measured by CT scanning (70). Similarly, AGE-modified proteins such as*N*-(carboxymethyl)lysine (CML), which

is abundantly present in the fibrotic lung tissue, have been implicated in the development of IPF (71). Also, accumulation of AGEs is found in alveolar macrophages of patients with IPF (72).

IMMUNOSENESCENSE

Immunosenescense is the term used to describe the natural alterations in the immune system with aging(73). There are two main clinical manifestations of immunosenescense:*(a)* impaired ability to fight infections and to respond to vaccinations in elderly individuals; and, *(b)* increased incidence of autoimmune diseases with age (74). Immunosenescense affect both the innate and acquired immune response. Accelerated immunosenescense occur both in COPD and IPF (Table 1).

Innate immune response and aging

Age related changes of the innate immune response involve both gain and loss of function in different cell types (75, 76). In general, the former are characterized by the presence of a persistent, low-grade pro-inflammatory environment, as shown by elevated levels of IL-6, TNF-α and acute phase reactants (*inflammaging*) (77), whereas the latter includes decreased functionality of specific innate immune effectors (75). Specific changes in the innate immune response with age include:*(a)* clonal expansion of myeloid progenitors at the expense of lymphoid progenitors (75). Circulating neutrophil levels do not increase with age, but neutrophil activity is altered, as shown by

impaired killing capacity, slower chemotaxis, and enhanced production of ROS ("*respiratory burst*") (78, 79);*(b)* circulating monocytes increase with age but their function decreases, partially due to toll-like receptor (TLR) deficient signaling (80, 81). Likewise, some reports indicate that macrophage function decrease with age, as shown by a reduced ability to produce cytokines *ex-vivo* in response to *Candida* antigens (82). Yet, others describe an enhanced production of ROS and bactericidal macrophage activity in aged mice(83). Thus it is conceivable that functional macrophage defects *ex vivo* can be restored in a pro-inflammatory milieu (84);*(c)* Dendritic cells (DCs) change their phenotype diversity and function with age, and their capacity to migrate to sites of infection and capture antigen is also reduced with aging (85). By contrast, their basal intracellular production of pro-inflammatory cytokines increases (86); and, *(d)* Natural killer (Nk) cells numbers increased with age due to the expansion of highly differentiated Nk cells (CD56 (dim) CD57+) with decreased proliferation and cytotoxicity capacity. These Nk cells have a lower ability to combat viral infections (74, 75, 79, 83) and may therefore contribute to morbidity and mortality in elderly individuals. Some of these changes appear to be amplified in patients with COPD and IPF(Table1)(87-90), including:*(a)* increased levels of neutrophils (91, 92); *(b)* increased numbers of monocytes and macrophages with modified pro-inflammatory cytokine production (92, 93); *(c)* altered DCs phenotype (94); and, *(d)* less active peripheral blood Nk cells in COPD (95).

Acquired immune response and aging

The acquired immune response also changes with age, including a reduction in the production of lymphocytes by primary lymphoid organs and modifications

lymphoid cell diversity and functionality (74, 96): (*a*) the thymus, where T cells develop, involutes with age. As a consequence, naïve T cells are reduced in blood and peripheral tissues of elderly individuals (97). By contrast, there is an expansion of memory cells, mostly highly differentiated CD8+ CD28 null cells, CD4+ cells and regulatory T cells. The final result is a T cell repertoire skewed toward previously encountered antigens (74, 75, 79) with less ability to respond to new infections; and, *(b)* B cell lymphopoiesis in the bone marrow declines in elderly subjects (98). Compared with B cells from younger individuals, antigens produced by B cells in aged humans exhibit decreased affinity for antigens and have an impaired ability to undergo class-switch recombination (99). Both changes modify the humoral immune response of the elderly. COPD and IPF patients share the following abnormal acquired immune responses (Table1): *(a)* a senescent T cell phenotype and a repertoire contraction (100, 101); and, *(b)* B memory cells are more frequent and have differential class switch recombination in COPD patients than in healthy individuals (102).

EXTRACELLULAR MATRIX (ECM) CHANGES INDUCED BY AGING

Collagen and elastin are the main proteins in the ECM that make up the framework of the alveolar structure, and are most important in determining the mechanical properties of lung parenchyma. In the lung, collagen represents 15 to 20% of the total dry weight of the pulmonary tissue; type I and III collagens (COL I to COL III, respectively) are the most representative of these, representing 90% of the total collagen. Another protein, fibronectin, forms fibrils associated with other matrix components and it has been implicated in cell

adhesion, migration, epithelial-mesenchymal transition (EMT), phagocytosis, and cell growth.

The composition of the ECM changes during aging (103) and contributes to the physiological decline of lung function with age (3, 6). Yet, it is unclear how age-dependent changes in ECM components affect lung repair. Fibronectin expression increases in clinical and experimental models of fibrosis. In injured lungs, during the early phase of active repair, fibronectin production increases dramatically, and this increase occurs at the same time as fibroblast proliferation, thereafter responsible for excessive synthesis and deposition of the collagen protein. Alterations in cell–fibronectin interactions may contribute to abnormal tissue remodeling by stimulating the proliferation of fibroblasts, myofibroblast differentiation, and EMT and by facilitating the deposition of other matrix components such as collagens. Fibronectin undergoes alternative splicing at each of the three fibronectin exons. Lungs from aging rats show a significant increase of the fibronectin isoform extra type III domain A (EDA). Growth factors are implicated in the regulation of fibronectin splicing; specifically, TGFβ1 up-regulatesfibronectin EDA expression. Fibronectin EDA is considered necessary for TGFβ1-induced myofibroblast differentiation. Furthermore, there is a higher proportion of fibronectin EDA protein in IPF patients when compared with controls, and lack of fibronectin EDA is protective against bleomycin-induced lung fibrosis in mice. Thus it is reasonable to propose that excessive expression, of fibronectin EDA, associated with age, in lung might promote fibrogenic responses in the setting of lung injury. Taken together, these observations indicate that aging leads to changes in the

expression of TGF-β and extracellular matrix composition. These changes are unique to the lung parenchyma and do not have a similar effect on the airways. Hence, their relevance for the pathogenesis of COPD is unclear but they can clearly contribute to explain, at least in part, the increased incidence of interstitial fibrotic lung disorders in elderly populations.

CONCLUSIONS

Many of the different cellular and molecular mechanisms of aging appear abnormal both in COPD and IPF. The reason why similar abnormalities of the ageing process result in different phenotypes (ie: IPF and COPD) is a key question to which currently there is no answer. With the current knowledge we can only speculate that as the ethiological factors driving these two diseases (mainly epithelial injury and others still unknown for IPF, and smoking for COPD) are different, they result in the mechanism of normal ageing being altered differently, in different sites or with different repair mechanisms/capacity. As a corollary, we propose that the ageing process is abnormal rather than accelerated in these patients, since these two diseases appear to be the result of defective and/or exhausted mechanisms of repair rather than their shift (accelerated aging) with early accumulations of these defects. In any case, a better understanding of these abnormalities may help designing novel and better therapeutic alternatives for patients suffering these devastating diseases.

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FIGURE LEGENDS

Figure 1. Regulation of senescence and the development of emphysema. Oxidative stress generated exogenously from cigarette smoke or endogenously from Mitochondria or inflammatory cells leads to stress-induced premature sencesence. Aging itself results in increase inflammation which results in increased cell turnover and hence increased replicative sensecence. Cellular senescence in COPD is also influenced by changes in insulin signalling and by decrease in antiaging molecules such as sirtuins. Cellular senescence results in reduced cellular proliferation, which together with increased proteolytic activity results in alveolar cell destruction and emphysema. For further explanations, see text.

Figure 2. Schematic representation of the mechanisms by which aged B-MSCs (mesenchymal stem cells) increase the susceptibility to the development of fibrosis due to senescence and exhaustion of the stem cells. This hypothesis is supported by the observation that aging B-MSCs, accumulate damage in their DNA, have a decrease on their response to soluble factors, resulting in a decrease on their ability to repair damaged organs. These observations are providing novel mechanisms to account for the higher incidence of chronic fibrosing lung disorders in subjects exposed to tobacco, asbestos, and other agents known to stimulate DNA damage.

Table 1. Mechanisms of aging that can participate in the pathogenesis COPD and IPF. For further explanations, see text.

Mechanism	Aging	COPD	IPF
Oxidative stress	Neutrophils, macrophages and monocytes show enhanced ROS production (78, 79). Telomere shortening is enhanced by oxidative stress (21, 104).	Increased oxidative stress in the lungs promoting inflammation (14-16, 105).	Increased oxidative stress in the lungs related to injury and fibrogenesis (17, 18).
Telomere Length (TL)	Decreased TL in peripheral blood leukocytes (PBLs) (106).	TL is smoking dose dependent. TL is shorter in PBLs in COPD and in emphysema (24, 104, 107).	Telomerase mutations are found in familiar pulmonary fibrosis (FPF) and sporadic IPF. (29, 30, 108).
Tissue specific cellular senescence	Induced when a critical telomere length is reached (109).	Elevated SA-ß-gal, p21 $^{CIP1/WAP1/sdi1}$ and pro-inflammatory cytokine production in lung parenchyma and type II alveolar cells (26, 34).	
Senescent Bone marrow-derived MSCs stem cells			Senescent B-MSCs and Fibrocytes increase the susceptibility to IPF due to abnormal lung repair (43, 44, 110, 111).
Anti aging molecules	The expression of Klotho in CD4+ lymphocytes decreases with age (112).	Knock-out mice models of SMP30 and Klotho develop accelerated aging and emphysema (57). Decreased levels of SIRT-1, HDAC2 are found in the lung of COPD patients (65).	
Advanced glycation end	Accumulation and binding of AGEs to	COPD patients have lower levels of	AGE-modified proteins are possible

product (AGE) accumulation	their receptor initiates cellular signals promotepro-inflammatory cytokines (113).	circulating AGEs correlating with the presence of emphysema (70).	pathogenic factors implicated in IPF, found in Alveolar Macrophages of patients (114).
Inflammatory cytokines	Persistent low level inflammation: IL-6, TNF-α and acute phase reactants (77).	Systemic and pulmonary increased levels of IL-6, TNF-a & CRP (87, 88).	Mild inflammation with IL-8, IL-6, CCL2 (89, 90).
Neutrophils	Unchanged numbers & impaired killing (78).	Increased in BALF and lung parenchyma (115).	Mild increase in BALF (92).
Macrophages/Monocytes	Deficient TLR signaling, less production of pro-inflammatory cytokines (79-81).	Increased in airways and lung parenchyma & production of pro-inflammatory cytokines (115).	Mild increase in BALF (92). Higher production of CCL18, IL8, CCL2, S100A9 and MIF (93).
NK cells	Increased numbers of highly differentiated NK cellsless active (74, 75, 79, 83).	Peripheral blood NK cells are less active and have less phagocytic activity (95).	
DCs	Change phenotype, increase the levels of pro-inflammatory cytokines (85, 86).	More active in COPD (116).	
T Cells	The proportion of memory cells with CD28null (senescent phenotype) increases and decreases the numbers of naïve T cells (97).	Senescent T cell phenotype and repertoire contraction (100). Less ability to fight infections.	Increased numbers of senescent T cell phenotype producing Th2 cytokines (101) considered pro-fibrotic.
B Cells	Decreased B cell production and impaired ability to Immunoglobulin class-switch (99).	B memory cells are more frequent in COPD patients, and have differential class switch recombination (91, 99).	
Extracellular matrix (ECM) changes		Alterations in ECM composition lead to abnormal tissue remodeling (3, 6).	Alterations in ECM composition and TGF-βlead to abnormal tissue remodeling (3, 6).

Figure 1.

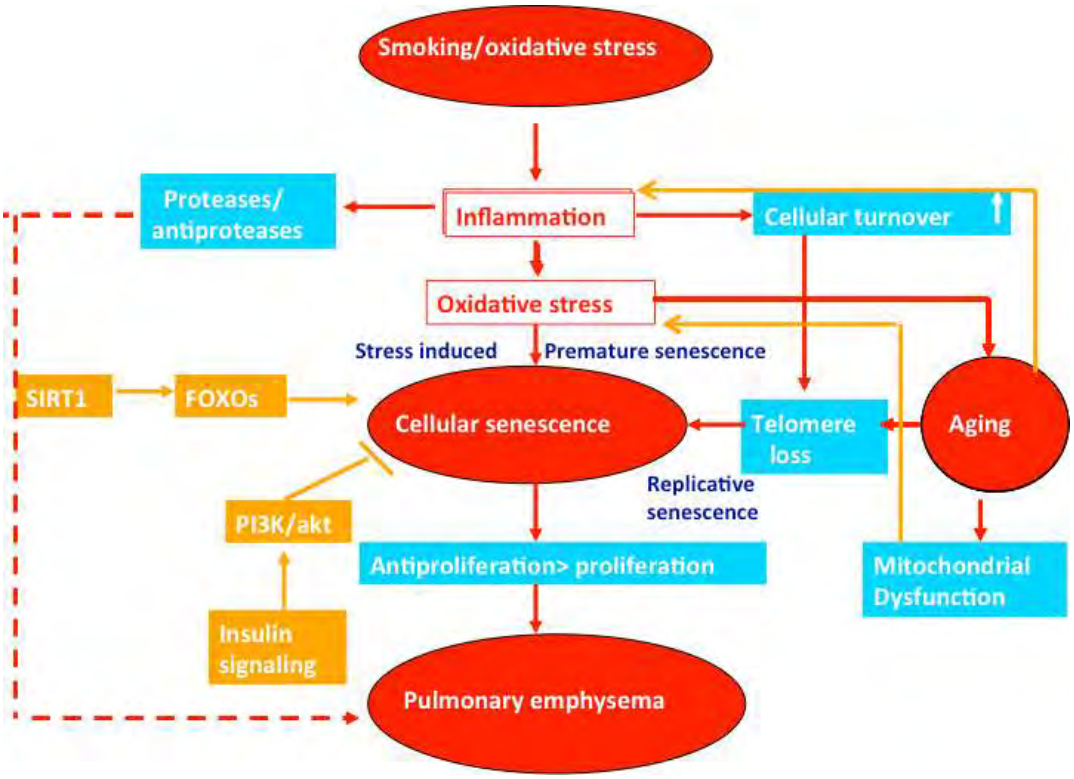
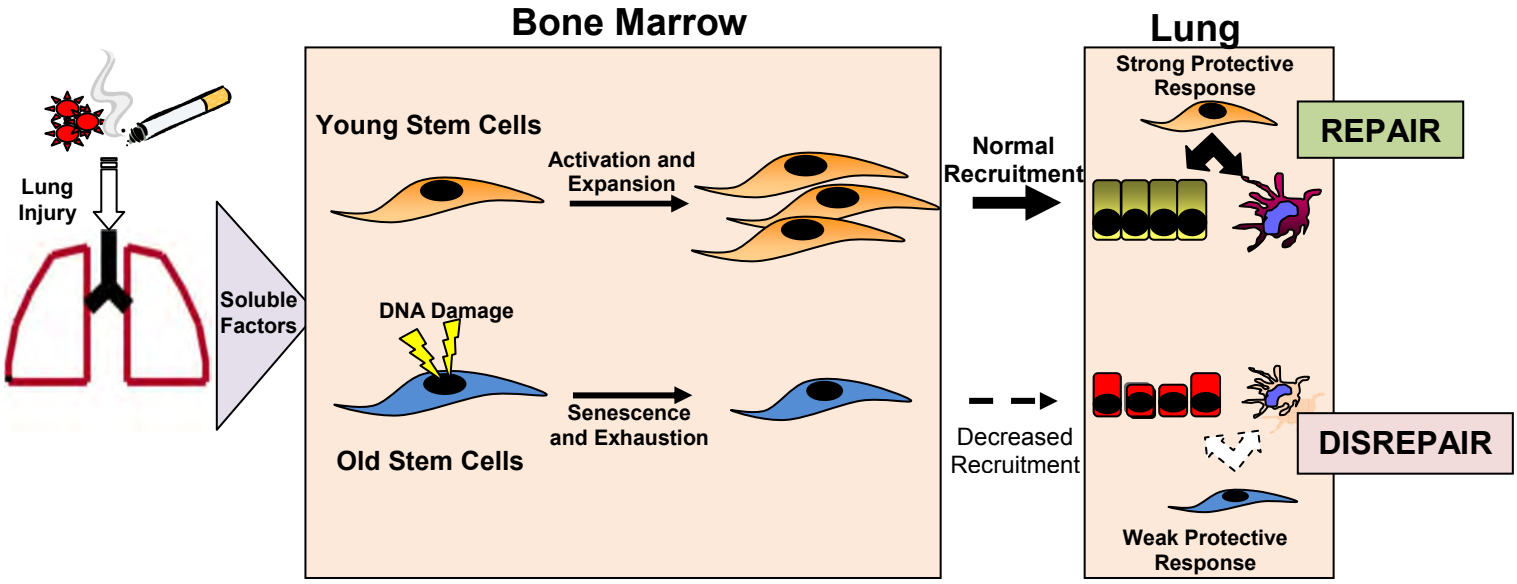

Smoking/oxidative stress
Proteases/ antiproteases
Inflammation
Cellular turnover
Oxidative stress
Stress induced
Premature senescence
SIRT1
FOXOs
Cellular senescence
Telomere loss
Aging
Replicative senescence
PI3K/akt
Antiproliferation> proliferation
Mitochondrial Dysfunction
Insulin signaling
Pulmonary emphysema

Figure Two


Bone Marrow
Lung
Lung Injury
Soluble Factors
Young Stem Cells
Activation and Expansion
DNA Damage
Senescence and Exhaustion
Old Stem Cells
Normal Recruitment
Decreased Recruitment
Strong Protective Response
REPAIR
DISREPAIR
Weak Protective Response